# Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer

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Abstract: BACKGROUND: Osimertinib is an oral, third-generation, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that selectively inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations. We compared osimertinib with standard EGFR-TKIs in patients with previously untreated, EGFR mutation-positive advanced non-small-cell lung cancer (NSCLC). METHODS: In this double-blind, phase 3 trial, we randomly assigned 556 patients with previously untreated, EGFR mutation-positive (exon 19 deletion or L858R) advanced NSCLC in a 1:1 ratio to receive either osimertinib (at a dose of 80 mg once daily) or a standard EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily). The primary end point was investigator-assessed progression-free survival. RESULTS: The median progression-free survival was significantly longer with osimertinib than with standard EGFR-TKIs (18.9 months vs. 10.2 months; hazard ratio for disease progression or death, 0.46; 95% confidence interval [CI], 0.37 to 0.57; P<0.001). The objective response rate was similar in the two groups: 80% with osimertinib and 76% with standard EGFR-TKIs (odds ratio, 1.27; 95% CI, 0.85 to 1.90; P=0.24). The median duration of response was 17.2 months (95% CI, 13.8 to 22.0) with osimertinib versus 8.5 months (95% CI, 7.3 to 9.8) with standard EGFR-TKIs. Data on overall survival were immature at the interim analysis (25% maturity). The survival rate at 18 months was 83% (95% CI, 78 to 87) with osimertinib and 71% (95% CI, 65 to 76) with standard EGFR-TKIs (hazard ratio for death, 0.63; 95% CI, 0.45 to 0.88; P=0.007 [nonsignificant in the interim analysis]). Adverse events of grade 3 or higher were less frequent with osimertinib than with standard EGFR-TKIs (34% vs. 45%). CONCLUSIONS: Osimertinib showed efficacy superior to that of standard EGFR-TKIs in the first-line treatment of EGFR mutation-positive advanced NSCLC, with a similar safety profile and lower rates of serious adverse events. (Funded by AstraZeneca; FLAURA ClinicalTrials.gov number, NCT02296125 .).

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# Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

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## ABSTRACT

### BACKGROUND

Osimertinib is an oral, third-generation, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that selectively inhibits both EGFR-TKI–sensitizing and *EGFR* T790M resistance mutations. We compared osimertinib with standard EGFR-TKIs in patients with previously untreated, *EGFR* mutation–positive advanced non–small-cell lung cancer (NSCLC).

### METHODS

In this double-blind, phase 3 trial, we randomly assigned 556 patients with previously untreated, *EGFR* mutation–positive (exon 19 deletion or L858R) advanced NSCLC in a 1:1 ratio to receive either osimertinib (at a dose of 80 mg once daily) or a standard EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily). The primary end point was investigator-assessed progression-free survival.

### RESULTS

The median progression-free survival was significantly longer with osimertinib than with standard EGFR-TKIs (18.9 months vs. 10.2 months; hazard ratio for disease progression or death, 0.46; 95% confidence interval [CI], 0.37 to 0.57; P<0.001). The objective response rate was similar in the two groups: 80% with osimertinib and 76% with standard EGFR-TKIs (odds ratio, 1.27; 95% CI, 0.85 to 1.90; P=0.24). The median duration of response was 17.2 months (95% CI, 13.8 to 22.0) with osimertinib versus 8.5 months (95% CI, 7.3 to 9.8) with standard EGFR-TKIs. Data on overall survival were immature at the interim analysis (25% maturity). The survival rate at 18 months was 83% (95% CI, 78 to 87) with osimertinib and 71% (95% CI, 65 to 76) with standard EGFR-TKIs (hazard ratio for death, 0.63; 95% CI, 0.45 to 0.88; P=0.007 [nonsignificant in the interim analysis]). Adverse events of grade 3 or higher were less frequent with osimertinib than with standard EGFR-TKIs (34% vs. 45%).

### CONCLUSIONS

Osimertinib showed efficacy superior to that of standard EGFR-TKIs in the first-line treatment of *EGFR* mutation–positive advanced NSCLC, with a similar safety profile and lower rates of serious adverse events. (Funded by AstraZeneca; FLAURA ClinicalTrials.gov number, NCT02296125.)

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*A list of the FLAURA Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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The current standard of care for patients with locally advanced or metastatic non–small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI)–sensitizing mutations is treatment with a first-generation or second-generation EGFR-TKI such as gefitinib, erlotinib, or afatinib.[1,2] Treatment with EGFR-TKIs in this patient population has extended progression-free survival relative to chemotherapy as initial therapy[3-5]; a meta-analysis of six randomized trials involving patients who had not previously received treatment showed a median progression-free survival of 11.0 months with EGFR-TKIs (gefitinib or erlotinib) versus 5.6 months with chemotherapy.[6] The phase 3 studies of first-generation and second-generation EGFR-TKIs showed a median progression-free survival of 9 to 13 months,[3-5,7-10] and the *EGFR* p.Thr790Met point mutation (*EGFR* T790M) is detected in 50% or more of the patients who have disease progression.[11,12]

Osimertinib is an oral, third-generation, irreversible EGFR-TKI that selectively inhibits both EGFR-TKI–sensitizing and *EGFR* T790M resistance mutations, with lower activity against wild-type *EGFR*.[13,14] On the basis of positive results from the AURA clinical program,[15-17] osimertinib is approved worldwide for the treatment of patients with metastatic T790M-positive NSCLC who have disease progression during or after EGFR-TKI therapy. Preclinical data support the ability of osimertinib to cross the blood–brain barrier and penetrate the central nervous system (CNS).[18] Previous studies in which osimertinib was given as a second-line treatment have shown superior efficacy in the CNS as compared with platinum chemotherapy.[15,19]

Preclinical data[13,20,21] and phase 1 clinical data from the AURA trial[22] suggest that osimertinib may also be an effective first-line therapy for patients with *EGFR* mutation–positive advanced NSCLC. A median progression-free survival of 20.5 months was recently reported in a group of 60 patients with previously untreated *EGFR* mutation–positive advanced NSCLC who received osimertinib (80 mg or 160 mg daily).[22] The phase 3 FLAURA trial assessed the efficacy and safety of osimertinib in patients with previously untreated *EGFR* mutation–positive advanced NSCLC as compared with the standard EGFR-TKIs, gefitinib or erlotinib.

## Methods

### Trial Patients

Patients had locally advanced or metastatic NSCLC, had not previously received treatment for advanced disease, and were eligible to receive first-line treatment with gefitinib or erlotinib. Local or central confirmation of the *EGFR* exon 19 deletion (Ex19del) or p.Leu858Arg (L858R) *EGFR* mutation, alone or co-occurring with other *EGFR* mutations, was required. Patients with CNS metastases whose condition was neurologically stable were eligible. Any previous definitive treatment or glucocorticoid therapy had to be completed at least 2 weeks before initiation of the trial treatment. Complete eligibility criteria are provided in the trial protocol, available with the full text of this article at NEJM.org.

### Trial Oversight

The trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Conference on Harmonisation), applicable regulatory requirements, and the policy on bioethics and human biologic samples of the trial sponsor, AstraZeneca. This trial was funded by the sponsor and was designed by the principal investigators (the first and last authors) and the sponsor. The sponsor was responsible for the collection and analysis of the data and had a role in data interpretation. The authors vouch for the completeness and accuracy of the data and the data analyses and adherence to the protocol. The first draft of the manuscript was written by the first and last authors, with medical-writing support funded by the sponsor; all the authors reviewed the manuscript, provided input, and made the decision to submit the manuscript for publication. The authors had full access to the data in the trial. The protocol, amendments, and statistical analysis plan are available at NEJM.org.

### Trial Design and Treatment

In this double-blind, phase 3 trial, patients were stratified according to tumor *EGFR* mutation status (Ex19del or L858R) and race (Asian or non-Asian) and were randomly assigned in a 1:1 ratio to receive either oral osimertinib (at a dose of 80 mg once daily) or a standard oral EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlo-

tinib at a dose of 150 mg once daily). Treatment continued until disease progression, the development of unacceptable side effects, or withdrawal of consent. Treatment beyond the point of disease progression (as assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) was allowed as long as there was continued clinical benefit, as judged by the investigator. A protocol amendment on April 13, 2015, allowed patients who had been assigned to a standard EGFR-TKI to cross over to open-label osimertinib after confirmation of objective disease progression by blinded independent central review and post-progression documentation of T790M-positive mutation status by means of plasma or tissue testing (local or central). Intervening anticancer therapy was not allowed before crossover to open-label osimertinib.

### TRIAL END POINTS

The primary end point was the duration of progression-free survival as determined by investigator assessments, according to RECIST, version 1.1. A sensitivity analysis of progression-free survival was performed on the basis of data from blinded independent central review of RECIST assessments for all the patients. Secondary end points included overall survival, the objective response rate, the duration of response, the disease-control rate (rate of complete response, partial response, or stable disease lasting ≥6 weeks before any disease-progression event), the depth of response (change in target-lesion size from baseline), and safety.

### TRIAL ASSESSMENTS

Tumor assessments occurred at baseline, every 6 weeks (±1 week) for 18 months, then every 12 weeks (±1 week) until disease progression. Baseline brain imaging was mandated only in patients with known or suspected CNS metastases, with follow-up imaging in patients with confirmed CNS metastases.

Progression-free survival was defined as the time from randomization to objective disease progression or death from any cause in the absence of progression, irrespective of withdrawal from the trial or treatment with another anticancer therapy before progression. Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Additional details on tumor assessments, secondary efficacy end points, and assessment of adverse events are included in the Supplementary Appendix, available at NEJM.org.

### STATISTICAL ANALYSIS

The full analysis set included all randomly assigned patients and was used for efficacy assessments. Adverse events were assessed in the safety analysis set, consisting of all the patients who received at least one dose of randomly assigned treatment.

A log-rank test, stratified according to race (Asian vs. non-Asian) and mutation type (Ex19del vs. L858R), was used to compare progression-free survival between treatment groups, with application of the Breslow approach to handle tied events. Data for patients who had not had a progression event or had not died at the time of the analysis were censored at the time of the last RECIST assessment that could be evaluated.

We determined that approximately 359 events of progression or death in a total of 530 randomly assigned patients would provide at least 90% power to detect a hazard ratio of 0.71 at a two-sided alpha level of 5%. The data cutoff date was June 12, 2017.

## RESULTS

### PATIENTS AND TREATMENT

From December 2014 through March 2016, a total of 994 patients were screened, across 132 sites in 29 countries, and 556 were randomly assigned to trial treatment (279 to osimertinib and 277 to a standard EGFR-TKI) (Fig. S1 and Table S1 in the Supplementary Appendix). Baseline characteristics were well balanced between the trial groups and in line with the intended population per the protocol (Table 1). All randomly assigned patients received at least one dose of trial treatment. At the time of data cutoff, the median duration of total treatment exposure was 16.2 months (range, 0.1 to 27.4) for patients receiving osimertinib and 11.5 months (range, 0 to 26.2) for those receiving a standard EGFR-TKI. A total of 141 patients (51%) in the osimertinib group and 64 (23%) in the standard EGFR-TKI group continued to receive trial treatment.

At the time of data cutoff, an event of RECIST-defined progression or death had occurred in

136 patients (49%) in the osimertinib group and 206 (74%) in the standard EGFR-TKI group. The percentage of patients who continued treatment beyond RECIST-defined progression was similar in the two groups (67% in the osimertinib group and 70% in the standard EGFR-TKI group).

After RECIST-defined progression, 82 patients (29%) in the osimertinib group and 129 (47%) in the standard EGFR-TKI group started a first subsequent anticancer therapy. Of these, 55 patients (43%) in the standard EGFR-TKI group received osimertinib (48 on crossover and 7 outside of the trial as second-line treatment). Further details on crossover and subsequent anticancer therapy are available in the Supplementary Appendix, including in Tables S2 and S3.

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.***

| Characteristic | Osimertinib (N = 279) | Standard EGFR-TKI (N = 277) |
|---|---|---|
| Age — yr | | |
| Median | 64 | 64 |
| Range | 26–85 | 35–93 |
| Male sex — no. (%) | 101 (36) | 105 (38) |
| Race — no. (%)† | | |
| White | 101 (36) | 100 (36) |
| Asian | 174 (62) | 173 (62) |
| Other | 4 (1) | 4 (1) |
| Smoking status — no. (%) | | |
| Never | 182 (65) | 175 (63) |
| Current | 8 (3) | 9 (3) |
| Former | 89 (32) | 93 (34) |
| WHO performance status — no. (%)‡ | | |
| 0 | 112 (40) | 116 (42) |
| 1 | 167 (60) | 160 (58) |
| Missing data | 0 | 1 (<1) |
| Histologic type — no. (%) | | |
| Adenocarcinoma | 275 (99) | 272 (98) |
| Other§ | 4 (1) | 5 (2) |
| Overall disease classification — no. (%) | | |
| Metastatic¶ | 264 (95) | 262 (95) |
| Locally advanced‖ | 14 (5) | 15 (5) |
| Missing data | 1 (<1) | 0 |
| Metastases — no. (%) | | |
| Visceral metastases** | 94 (34) | 103 (37) |
| CNS metastases†† | 53 (19) | 63 (23) |
| *EGFR* mutation type at randomization — no. (%) | | |
| Exon 19 deletion | 175 (63) | 174 (63) |
| L858R | 104 (37) | 103 (37) |
| *EGFR* mutation type by central test — no. (%)‡‡ | | |
| Exon 19 deletion | 158 (57) | 155 (56) |
| L858R | 97 (35) | 90 (32) |
| No mutation detected, invalid test, or no or inadequate sample | 24 (9) | 32 (12) |

**Table 1. (Continued.)**

| Characteristic | Osimertinib (N=279) | Standard EGFR-TKI (N=277) |
|---|---|---|
| EGFR-TKI comparator — no. (%) | | |
| Gefitinib | NA | 183 (66) |
| Erlotinib | NA | 94 (34) |

* No formal comparison between the two groups was performed for baseline characteristics. CNS denotes central nervous system, EGFR-TKI epidermal growth factor receptor tyrosine kinase inhibitor, and NA not applicable. Percentages may not total 100 because of rounding.
† Race was reported by the patient. The category of "other" includes black, American Indian, and Alaska Native.
‡ The World Health Organization (WHO) performance status of 0 indicates that the patient is fully active and able to carry out all predisease activities without restrictions, and a WHO performance status of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work.
§ Five patients (two in the osimertinib group and three in the standard EGFR-TKI group) had large-cell carcinoma; three patients (one in the osimertinib group and two in the standard EGFR-TKI group) had adenosquamous carcinoma; and one patient (in the osimertinib group) had a carcinoid tumor.
¶ The patient had any metastatic site of disease.
‖ The patient had only locally advanced sites of disease.
** Visceral metastases were determined programmatically from baseline data for which the disease site was described as adrenal, ascites, brain or CNS, gastrointestinal, genitourinary, hepatic (including gallbladder), liver, other CNS, pancreas, peritoneum, or spleen. Also included were other metastatic sites, such as those occurring in the eye and thyroid, as identified as extrathoracic visceral sites by AstraZeneca physicians.
†† CNS metastases were determined programmatically from baseline data for the CNS lesion site, medical history, surgery, or radiotherapy.
‡‡ A patient could have more than one type of mutation.

### EFFICACY

The median progression-free survival was 18.9 months (95% confidence interval [CI], 15.2 to 21.4) in the osimertinib group and 10.2 months (95% CI, 9.6 to 11.1) in the standard EGFR-TKI group (Fig. 1A). The median duration of follow-up for progression-free survival was 15.0 months (range, 0 to 25.1) and 9.7 months (range, 0 to 26.1), respectively. Investigator-assessed progression-free survival was significantly longer in the osimertinib group than in the standard EGFR-TKI group (hazard ratio for disease progression or death, 0.46; 95% CI, 0.37 to 0.57; P<0.001). Kaplan–Meier event curves showed early separation between the two groups, at the time of the first assessment (at 6 weeks). Results for progression-free survival as determined by blinded independent central review were consistent with those for investigator-assessed progression-free survival and are provided in the Results section in the Supplementary Appendix, as are results for post-progression end points.

A consistent benefit of osimertinib over standard EGFR-TKIs with respect to progression-free survival was shown across all predefined subgroups that were assessed (Fig. 2), including the subgroups based on race (Asian vs. non-Asian), *EGFR* mutation type (Ex19del vs. L858R) (Fig. S3A and S3B in the Supplementary Appendix), and the presence or absence of known or treated CNS metastases at trial entry (Fig. 1B and 1C). Irrespective of status with respect to known or treated CNS metastases at trial entry, events of CNS progression were observed in 17 patients (6%) in the osimertinib group and 42 (15%) in the standard EGFR-TKI group (Table S4 in the Supplementary Appendix).

The objective response rate (with response assessed by the investigator) was 80% (95% CI, 75 to 85) in the osimertinib group and 76% (95% CI, 70 to 81) in the standard EGFR-TKI group (odds ratio, 1.27; 95% CI, 0.85 to 1.90; P=0.24) (Table 2). The disease-control rate was 97% (95% CI, 94 to 99) versus 92% (95% CI, 89 to 95), respectively (odds ratio, 2.78; 95% CI, 1.25 to 6.78; P=0.01). The median best percentage change in target-lesion size (maximum decrease from baseline, or minimum increase from baseline in the absence of a decrease) was –54.7% (range, –100 to 61.9) in the osimertinib group versus –48.5% (range, –100 to 54.1) in the standard EGFR-TKI group (P=0.003); more information on the depth of response is available in the Supplementary Appendix, including Figure S4.

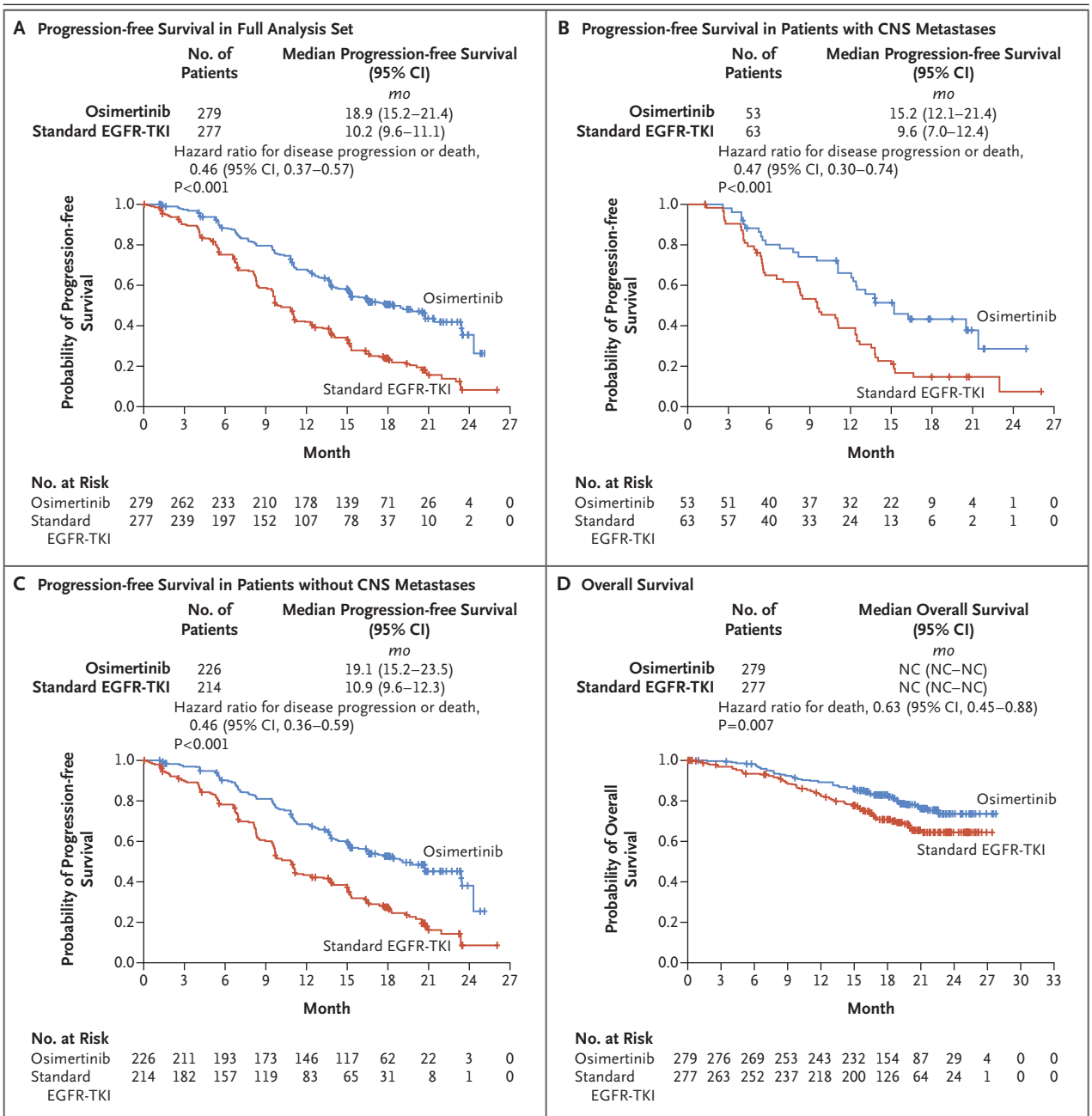


**Figure 1. Progression-free Survival and Overall Survival.**

Shown are Kaplan–Meier estimates of the duration of progression-free survival in the full analysis set as assessed by investigators (Panel A), in patients with known or treated central nervous system (CNS) metastases at trial entry (Panel B), and in patients without known or treated CNS metastases at trial entry (Panel C). Also shown are Kaplan–Meier estimates of overall survival (Panel D). Censored data are indicated by tick marks. For the analysis of progression-free survival, data for patients who had not had a progression event or had not died at the time of the analysis were censored at the time of their last assessment (according to Response Evaluation Criteria in Solid Tumors) that could be evaluated. For the analysis of overall survival, data for any patients who were not known to have died at the time of the analysis were censored at the last recorded date that the patient was known to be alive. CI denotes confidence interval, EGFR-TKI epidermal growth factor receptor tyrosine kinase inhibitor, and NC could not be calculated.

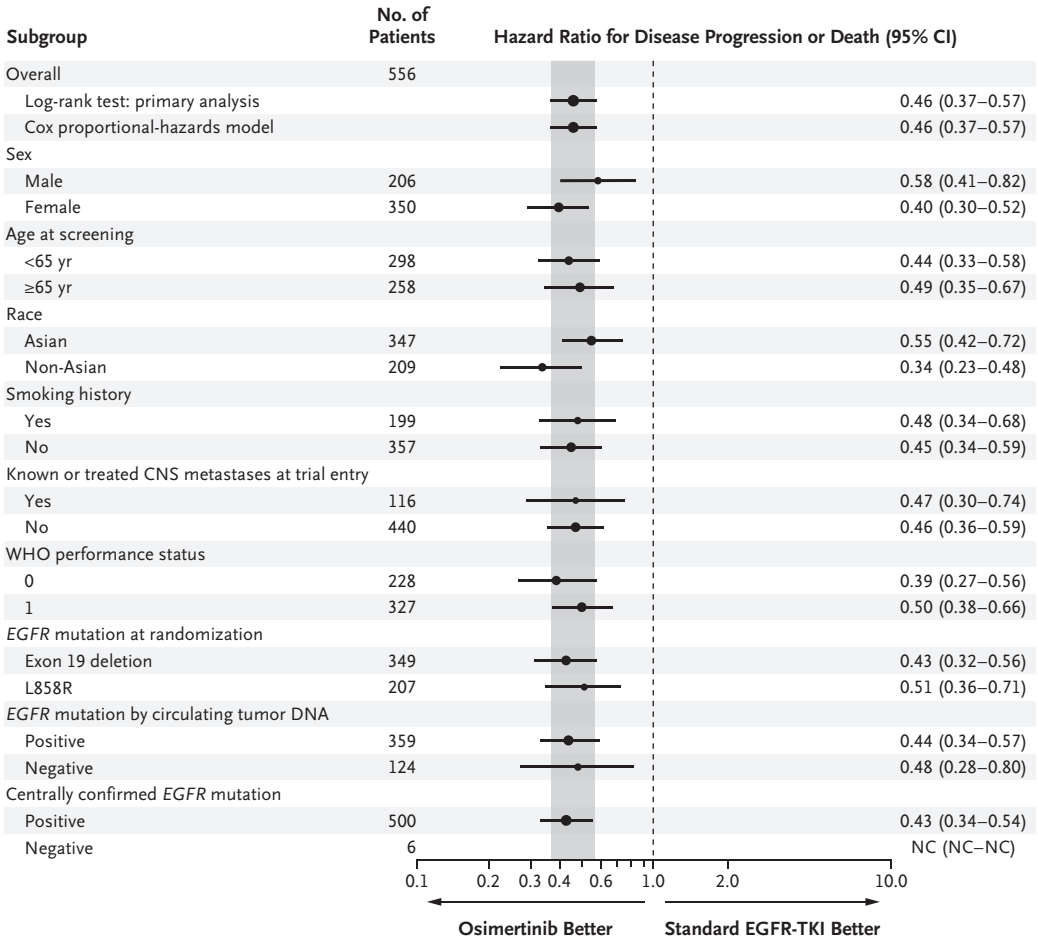


**Figure 2. Subgroup Analyses of Progression-free Survival.**

A hazard ratio of less than 1 implies a lower risk of disease progression or death with osimertinib than with standard EGFR-TKIs. The Cox proportional-hazards model includes randomly assigned treatment, the subgroup covariate of interest, and the treatment-by-subgroup interaction. The size of the circles is proportional to the number of events. Overall population analyses are presented from both a Cox proportional-hazards model and the primary analysis (U and V statistics from a log-rank test stratified according to *EGFR* mutation type and race). If there were fewer than 20 events in a subgroup, then the analysis was not performed. The shaded area indicates the 95% CI for the overall hazard ratio (all patients). *EGFR* mutation status at randomization was determined by means of a local or central test. Data on World Health Organization (WHO) performance status were missing for 1 patient in the standard EGFR-TKI group. Data on *EGFR* mutation status determined in circulating tumor DNA were missing for 36 patients in the osimertinib group and 37 patients in the standard EGFR-TKI group. Data on centrally confirmed *EGFR* mutation status were missing for 21 patients in the osimertinib group and 29 patients in the standard EGFR-TKI group.

Among the patients who had a response to trial treatment, an event of disease progression or death had occurred in 106 of 223 patients (48%) in the osimertinib group and 158 of 210 (75%) in the standard EGFR-TKI group at the time of data cutoff. The median duration of response was longer in the osimertinib group (17.2 months [95% CI, 13.8 to 22.0]) than in the standard EGFR-TKI group (8.5 months [95% CI, 7.3 to 9.8]). In most cases, responses were documented at the time of the first scan, with a median time to response of 6.1 weeks (95% CI, 6.0 to 6.1) in the osimertinib

**Table 2. Secondary Efficacy End Points.***

| End Point | Osimertinib (N=279) | Standard EGFR-TKI (N=277) |
|---|---|---|
| Type of response — no. (%)† | | |
| Complete | 7 (3) | 4 (1) |
| Partial | 216 (77) | 206 (74) |
| Stable disease for ≥6 wk | 47 (17) | 46 (17) |
| Progression | 3 (1) | 14 (5) |
| Death | 0 | 5 (2) |
| Could not be evaluated | 6 (2) | 7 (3) |
| Objective response rate — % of patients (95% CI) | 80 (75–85) | 76 (70–81) |
| Disease-control rate — % of patients (95% CI)‡ | 97 (94–99) | 92 (89–95) |
| Time to response§ | | |
| No. of weeks — median (95% CI) | 6.1 (6.0–6.1) | 6.1 (NC–NC) |
| ≤6 wk after first dose — no./total no. (%) | 154/223 (69) | 148/210 (70) |
| ≤12 wk after first dose — no./total no. (%) | 193/223 (87) | 180/210 (86) |
| ≤18 wk after first dose — no./total no. (%) | 199/223 (89) | 196/210 (93) |
| Duration of response¶ | | |
| No. of months — median (95% CI) | 17.2 (13.8–22.0) | 8.5 (7.3–9.8) |
| Range | 0–23.8 | 0–24.9 |
| Percent of patients with continued response at 12 mo (95% CI) | 64 (58–70) | 37 (31–44) |
| Percent of patients with continued response at 18 mo (95% CI) | 49 (41–56) | 19 (13–26) |
| Percent of patients with continued response at 24 mo (95% CI) | NC (NC–NC) | 5 (1–16) |
| Overall survival‖ | | |
| No. of months — median (95% CI) | NC (NC–NC) | NC (NC–NC) |
| Percent of patients alive at 6 mo (95% CI) | 98 (96–99) | 93 (90–96) |
| Percent of patients alive at 12 mo (95% CI) | 89 (85–92) | 82 (77–86) |
| Percent of patients alive at 18 mo (95% CI) | 83 (78–87) | 71 (65–76) |

* Efficacy analyses included all randomly assigned patients (full analysis set). CI denotes confidence interval, and NC could not be calculated.
† Tumor responses were assessed by the investigators according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.
‡ The disease-control rate is the proportion of patients who had a complete response, a partial response, or stable disease lasting at least 6 weeks before any disease-progression event.
§ The time to tumor response was calculated with the use of the Kaplan–Meier method from the date of randomization to the date of the first documentation of a partial or complete response. Per the protocol, RECIST assessments occurred every 6 weeks (±1 week) for 18 months, then every 12 weeks (±1 week) until disease progression.
¶ The duration of response was calculated with the use of the Kaplan–Meier method from the date of the first documented response until the date of documented disease progression or death in the absence of disease progression.
‖ Overall survival was calculated from the date of randomization to the date of death due to any cause.

group and 6.1 weeks (neither limit of the 95% confidence interval could be calculated) in the standard EGFR-TKI group. In patients with known or treated CNS metastases at trial entry, the objective response rate (with response assessed by the investigator) and the median duration of response were in line with the values in the overall population (Table S5 in the Supplementary Appendix).

At the time of data cutoff, the median overall survival could not be calculated in either treatment group (data maturity, 25%). A higher percentage of patients in the osimertinib group than in the standard EGFR-TKI group were alive at 12 months and 18 months. At 18 months, the estimated percentage of patients who were alive was 83% (95% CI, 78 to 87) in the osimertinib group and

71% (95% CI, 65 to 76) in the standard EGFR-TKI group (Table 2). A total of 141 patients had died: 58 (21%) in the osimertinib group and 83 (30%) in the standard EGFR-TKI group (hazard ratio for death, 0.63; 95% CI, 0.45 to 0.88; P=0.007) (Fig. 1D). For statistical significance at this interim analysis of overall survival, a P value of less than 0.0015 (determined by the O'Brien–Fleming approach) was required.

### SAFETY AND ADVERSE EVENTS

Adverse events of grade 3 or higher were reported in fewer patients in the osimertinib group than in the standard EGFR-TKI group (34% vs. 45%). These events are summarized in Table S6 in the Supplementary Appendix.

The most commonly reported adverse events due to any cause (treatment-related or not) were rash or acne (58% in the osimertinib group and 78% in the standard EGFR-TKI group), diarrhea (58% and 57%, respectively), and dry skin (36% in each group) (Table 3). Adverse events that were considered by the investigator to be possibly related to a trial drug are reported in Table S7 in the Supplementary Appendix.

Cardiac effects (changes in QT interval) were reported in a higher percentage of patients in the osimertinib group (29 patients [10%]) than in the standard EGFR-TKI group (13 patients [5%]). Across groups, the majority of adverse events in this category were of grade 1 (11 patients [4%] in the osimertinib group and 7 [3%] in the standard EGFR-TKI group) or grade 2 (12 patients [4%] in the osimertinib group and 3 [1%] in the standard EGFR-TKI group). There were no fatal cases of torsades des pointes or prolongation of the QT interval in either treatment group. Analysis of prolongation of the QT interval that was identified on electrocardiography showed a baseline median QT interval corrected for heart rate according to Fridericia's formula (QTcF) of 411.8 msec in the osimertinib group and 408.0 msec in the standard EGFR-TKI group. In both treatment groups, a maximum change from baseline in the median QTcF was reported at week 12 (17.7 msec in the osimertinib group and 10.0 msec in the standard EGFR-TKI group), after which QTcF values remained generally stable across both groups. Further details on cardiac effects are provided in the Supplementary Appendix.

Adverse events of interstitial lung disease were reported in 11 patients (4%) in the osimertinib group and 6 (2%) in the standard EGFR-TKI group. No fatal events of interstitial lung disease were reported in either group. In the osimertinib group, the outcome of interstitial lung disease was reported as "recovered" for 7 of 11 patients and "recovering" for the remaining 4 patients. In the standard EGFR-TKI group, the outcome was reported as "recovered" for 4 of 6 patients, "recovering" for 1 patient, and "not recovered" for 1 patient.

Overall, serious adverse events were reported in 60 patients (22%) in the osimertinib group and 70 (25%) in the standard EGFR-TKI group (Table S8 in the Supplementary Appendix). One patient (in the osimertinib group) had a serious adverse event of prolongation of the QT interval. Serious adverse events of interstitial lung disease occurred in 6 patients in the osimertinib group and 4 in the standard EGFR-TKI group.

Fatal adverse events occurred in 6 patients (2%) in the osimertinib group (pneumonia, respiratory tract infection, cerebral infarction, myocardial infarction, pulmonary embolism, and intestinal ischemia in 1 patient each) and 10 patients (4%) in the standard EGFR-TKI group (sepsis in 2 patients; pneumonia in 1; endocarditis in 1; cognitive disorder and pneumonia in 1; peripheral-artery occlusion in 1; dyspnea in 1; hemoptysis in 1; diarrhea, gastrointestinal hemorrhage, respiratory failure, and circulatory collapse in 1; and "death" [the adverse event was not further specified] in 1). None of the fatal adverse events were considered to be possibly related to osimertinib, and one fatal adverse event (of diarrhea) was considered to be possibly related to standard EGFR-TKIs.

Osimertinib was associated with a somewhat lower rate of adverse events leading to permanent discontinuation than were standard EGFR-TKIs (in 37 patients [13%] and 49 patients [18%], respectively). The frequency of dose interruption (25% in the osimertinib group and 24% in the standard EGFR-TKI group) and dose reduction (4% and 5%, respectively) due to adverse events was similar in the two groups.

## DISCUSSION

The results of the FLAURA trial show that in patients with previously untreated *EGFR* mutation–positive advanced NSCLC, osimertinib treatment resulted in significantly longer progression-free survival than did standard EGFR-TKIs. The me-

**Table 3. Adverse Events.***

| Adverse Event | Osimertinib (N=279) | | | | | Standard EGFR-TKI (N=277) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| | *number of patients (percent)* | | | | | | | | | |
| Any adverse event | 273 (98) | 34 (12) | 144 (52) | 83 (30) | 6 (2) | 271 (98) | 22 (8) | 125 (45) | 103 (37) | 11 (4) |
| Rash or acne† | 161 (58) | 134 (48) | 24 (9) | 3 (1) | 0 | 216 (78) | 110 (40) | 87 (31) | 19 (7) | 0 |
| Diarrhea | 161 (58) | 120 (43) | 35 (13) | 6 (2) | 0 | 159 (57)‡ | 116 (42) | 35 (13) | 6 (2) | 0 |
| Dry skin† | 100 (36) | 87 (31) | 12 (4) | 1 (<1) | 0 | 100 (36) | 76 (27) | 21 (8) | 3 (1) | 0 |
| Paronychia† | 97 (35) | 52 (19) | 44 (16) | 1 (<1) | 0 | 91 (33) | 55 (20) | 34 (12) | 2 (1) | 0 |
| Stomatitis | 80 (29) | 65 (23) | 13 (5) | 1 (<1) | 1 (<1) | 56 (20) | 47 (17) | 8 (3) | 1 (<1) | 0 |
| Decreased appetite | 56 (20) | 27 (10) | 22 (8) | 7 (3) | 0 | 52 (19) | 25 (9) | 22 (8) | 5 (2) | 0 |
| Pruritus | 48 (17) | 40 (14) | 7 (3) | 1 (<1) | 0 | 43 (16) | 30 (11) | 13 (5) | 0 | 0 |
| Cough | 46 (16) | 34 (12) | 12 (4) | 0 | 0 | 42 (15) | 25 (9) | 16 (6) | 1 (<1) | 0 |
| Constipation | 42 (15) | 33 (12) | 9 (3) | 0 | 0 | 35 (13) | 28 (10) | 7 (3) | 0 | 0 |
| Nausea | 39 (14) | 28 (10) | 11 (4) | 0 | 0 | 52 (19)‡ | 32 (12) | 19 (7) | 0 | 0 |
| Fatigue | 38 (14) | 21 (8) | 15 (5) | 2 (1) | 0 | 33 (12) | 23 (8) | 8 (3) | 2 (1) | 0 |
| Dyspnea | 35 (13) | 24 (9) | 10 (4) | 1 (<1) | 0 | 20 (7)‡ | 8 (3) | 8 (3) | 3 (1) | 0 |
| Anemia | 34 (12) | 19 (7) | 12 (4) | 3 (1) | 0 | 25 (9) | 18 (6) | 4 (1) | 3 (1) | 0 |
| Headache | 33 (12) | 26 (9) | 6 (2) | 1 (<1) | 0 | 19 (7) | 12 (4) | 7 (3) | 0 | 0 |
| Vomiting | 31 (11) | 25 (9) | 6 (2) | 0 | 0 | 29 (10) | 22 (8) | 3 (1) | 4 (1) | 0 |
| Upper respiratory tract infection | 28 (10) | 16 (6) | 12 (4) | 0 | 0 | 18 (6) | 9 (3) | 9 (3) | 0 | 0 |
| Pyrexia | 28 (10) | 27 (10) | 1 (<1) | 0 | 0 | 11 (4) | 8 (3) | 2 (1) | 1 (<1) | 0 |
| Prolonged QT interval on ECG | 28 (10) | 11 (4) | 11 (4) | 5 (2) | 1 (<1) | 11 (4) | 6 (2) | 3 (1) | 2 (1) | 0 |
| Aspartate aminotransferase elevation | 26 (9) | 18 (6) | 6 (2) | 2 (1) | 0 | 68 (25) | 38 (14) | 18 (6) | 12 (4) | 0 |
| Alopecia | 20 (7) | 17 (6) | 3 (1) | 0 | 0 | 35 (13) | 31 (11) | 4 (1) | 0 | 0 |
| Alanine aminotransferase elevation | 18 (6) | 11 (4) | 6 (2) | 1 (<1) | 0 | 75 (27) | 31 (11) | 19 (7) | 21 (8) | 4 (1) |

* Listed are adverse events that were reported in at least 10% of the patients in any group. Safety analyses included all the patients who received at least one dose of a trial drug (safety analysis set). Some patients had more than one adverse event. ECG denotes electrocardiography.

† This category represents a grouped term for the event. If a patient had multiple preferred-term events within a specific grouped-term adverse event, then the maximum grade (according to the Common Terminology Criteria for Adverse Events) across those events was counted.

‡ In the standard EGFR-TKI group, there were two patients who had missing data on grade, one with diarrhea and one with nausea. In addition, there was one patient with grade 5 diarrhea and one patient with grade 5 dyspnea.

dian progression-free survival in the osimertinib group was 18.9 months, with a 54% lower risk of disease progression or death than in the standard EGFR-TKI group. Although there was no statistical comparison of safety data, the safety profile of osimertinib was similar to that of standard EGFR-TKIs, but with somewhat lower rates of adverse events of grade 3 or higher, despite a longer median duration of exposure with osimertinib. These data suggest that osimertinib is superior to current standard EGFR-TKIs as first-line therapy.[3-5,23]

Our trial population had demographic and clinical characteristics that were in line with those of the global population of patients with *EGFR* mutation–positive advanced NSCLC. The progression-free survival benefit with osimertinib was observed across all predefined patient subgroups, including in patients with or without known or treated CNS metastases at trial entry. This finding is consistent with those of previous reports showing both systemic and CNS efficacy of osimertinib in patients with T790M-positive NSCLC and CNS metastases.[15,17] Patients with NSCLC who have CNS metastases tend to have a worse prognosis than those who have no such metastases,[24] and although early-generation EGFR-TKIs show better CNS efficacy than chemotherapy, a high frequency of CNS disease progression has been reported.[25,26] In our trial, the frequency of events of CNS progression at the time of this analysis was lower in the osimertinib group than in the standard EGFR-TKI group. However, some cases of asymptomatic progression may not have been detected, because only patients with brain metastases were required to have regular brain scans.

The median progression-free survival in the standard EGFR-TKI group in our trial is consistent with that in previous clinical trials of earlier-generation EGFR-TKIs (approximately 9 to 13 months).[3-5] Recently, the ARCHER 1050 trial (dacomitinib vs. gefitinib) showed a superior median progression-free survival with dacomitinib, an investigational EGFR inhibitor, in patients with previously untreated *EGFR* mutation–positive advanced NSCLC.[27] Patients with brain metastases were excluded from that trial.

At this interim analysis of overall survival (data maturity, 25%), the overall survival benefit did not reach formal statistical significance for osimertinib. However, the initial signal for a potential survival benefit with osimertinib (hazard ratio for death, 0.63) is encouraging and is supported by the early separation of the Kaplan–Meier curves of overall survival.

The most common mechanism of resistance to early-generation EGFR-TKIs when they are used as first-line therapy is the T790M mutation[11,12]; other resistance mechanisms that have been reported include amplification of *HER2*, *MET*, and *MAPK1*; mutation of *PIK3CA* and *BRAF*; and small-cell transformation.[28] Mechanisms of resistance to osimertinib that have been identified in patients with T790M-positive NSCLC after EGFR-TKI treatment include acquired *EGFR* mutations (e.g., C797S), *MET* and *HER2* amplification, and small-cell transformation.[29-32] Mechanisms of resistance to osimertinib when used as first-line therapy remain to be fully characterized, although an analysis of genomic mechanisms of resistance in nine patients with previously untreated *EGFR* mutation–positive advanced NSCLC who received osimertinib in the phase 1 component of the AURA trial showed no cases of acquired T790M mutation.[22] Tissue-based analyses of resistance mechanisms will be necessary to fully characterize resistance to osimertinib. Analysis of post-progression plasma samples from participants in our trial may provide additional insights into mechanisms of resistance. The early separation of the Kaplan–Meier curves of progression-free survival (at the time of the first assessment, at 6 weeks) in our trial could indicate a lower frequency of early resistance to osimertinib than of early resistance to standard EGFR-TKIs as first-line therapy. In the ARCHER 1050 trial (dacomitinib vs. gefitinib) and the LUX-Lung 7 trial (afatinib vs. gefitinib), the Kaplan–Meier curves of progression-free survival separated at approximately 6 and 11 months, respectively,[23,27] findings that suggest the presence of a subpopulation of patients in both treatment groups with intrinsic or early acquired resistance to a trial drug.

Our trial had several strengths. These include a double-blind trial design, the enrollment of patients worldwide, the use of the two most commonly used EGFR-TKIs for the standard EGFR-TKI group, independent verification of radiographic outcomes to confirm the results derived from investigator assessment, central confirmation of mutation status in the majority of the patients, the inclusion of patients with CNS metastases, and the option to cross over to osimertinib for patients with T790M-positive tumors after progression during standard EGFR-TKI therapy.

A limitation of the trial is the exclusion of afatinib from the comparator group. At the time of trial initiation, afatinib was not widely used and had not been made available as a global standard-of-care EGFR-TKI. However, clinical outcomes with afatinib are well characterized, and a recent meta-analysis concludes that there is no difference in efficacy among afatinib, erlotinib, and gefitinib.[33] A further limitation is that magnetic resonance imaging of the head was not mandated for all the patients. This limits the ability to detect asymptomatic brain metastases.

In conclusion, osimertinib treatment resulted in longer progression-free survival than did current standard first-line therapy for *EGFR* mutation–positive NSCLC, with a similar safety profile.

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## APPENDIX

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